Bile Acids and Farnesoid X Receptor: Novel Target for the Treatment of Diabetic Cardiomyopathy

Li, Chao ; Li, Yunlun ; Gai, Zhibo

Abstract: Diabetes mellitus (DM) has become an increasingly common disease with high disability and mortality rates. Diabetes complications are the main cause of diabetes death and about 50% of diabetic patients died from heart disease in developed countries reported by World Health Organization. Diabetic cardiomyopathy (DCM) has been considered as a high incidence and serious complication of DM and plays a key role in the incidence and development of diabetes related heart failure. Metabolism dysregulation is regarded as an important and earlier factor occurred in the pathogenesis of DCM. Insulin resistance, oxidative stress, inflammation and mitochondrial dysfunction also contribute to the development of DCM. Farnesoid X Receptor (FXR) is a member of nuclear receptor superfamily, and plays a critical role in regulating lipid and glucose metabolism, oxidative stress and inflammation. FXR is activated by primary bile acids (BAs) such as chenodeoxycholic acid, cholic acid and synthetic agonists such as obeticholic acid. BAs are the main active ingredients of many natural products and traditional medicines, especially bile or gallstones in animals, such as calculus bovis. Due to the regulatory effect of FXR on glucose and lipid metabolism, oxidative stress and inflammation, the treatment of BAs and FXR agonists for metabolic syndrome and DCM have gained more attention. This review will focus on the pathogenesis of diabetic cardiomyopathy and the regulatory effect of BAs and FXR on DCM.

DOI: https://doi.org/10.2174/1389203720666190726152847

Bile Acids and Farnesoid X Receptor: Novel Target for the Treatment of Diabetic Cardiomyopathy

Abstract: Diabetes mellitus (DM) has become an increasingly common disease with high disability and mortality rates. Diabetes complications are the main cause of diabetes death and about 50% of diabetic patients died from heart disease in developed countries reported by World Health Organization. Diabetic cardiomyopathy (DCM) has been considered as a high incidence and serious complication of DM and plays a key role in the incidence and development of diabetes related heart failure. Metabolism dysregulation is regarded as an important and earlier factor occurred in the pathogenesis of DCM. Insulin resistance, oxidative stress, inflammation and mitochondrial dysfunction also contribute to the development of DCM. Farnesoid X Receptor (FXR) is a member of nuclear receptor superfamily, and plays a critical role in regulating lipid and glucose metabolism, oxidative stress and inflammation. FXR is activated by primary bile acids (BAs) such as chenodeoxycholic acid, cholic acid and synthetic agonists such as obeticholic acid. BAs are the main active ingredients of many natural products and traditional medicines, especially bile or gallstones in animals, such as calculus bovis. Due to the regulatory effect of FXR on glucose and lipid metabolism, oxidative stress and inflammation, the treatment of BAs and FXR agonists for metabolic syndrome and DCM have gained more attention. This review will focus on the pathogenesis of diabetic cardiomyopathy and the regulatory effect of BAs and FXR on DCM.

Keywords: Bile Acids, farnesoid X receptor, diabetic cardiomyopathy, oxidative stress, inflammation, mitochondrial dysfunction.

Running title: Bile Acids and Farnesoid X Receptor in Diabetic Cardiomyopathy

1. INTRODUCTION

Diabetes mellitus (DM) has become a global health problem and the prevalence of diabetes has been increasing at a fast speed owing to changes of dietary and the sedentary lifestyle. It was estimated that 451 million people (8.4% of the world population) lived with diabetes in 2017 and the number was predicted to rise to 693 million by 2045 [1]. People with diabetes have a much higher risk of developing cardiovascular complications. Diabetic cardiovascular disease has been considered as the major cause of diabetes mortality, and about 50% of diabetic patients died from heart disease in developed countries reported by the World Health Organization [2]. Diabetic cardiomyopathy (DCM) is a high incidence and serious complication of diabetes and often evolves to diabetes related heart failure. DCM was first described by Rubler [3] in 1972 and further confirmed by the well-known Framingham study in 1974 which showed a four to five fold increased risk of congestive heart failure in diabetic patients even after excluding coronary or rheumatic heart disease [4]. DCM is characterized by the abnormal myocardial structural and cardiac dysfunction in the absence of hypertension, coronary artery disease and other cardiac risk factors [5]. The pathogenesis of DCM is complex and multifactorial, including altered substrate metabolism, oxidative stress, inflammation, insulin resistance and mitochondrial dysfunction [5, 6]. Microvascular dysfunction [7, 8], altered calcium handling [9] and accumulation of advanced glycation end-products [10] also implicated in different stages of DCM resulting in cardiac dysfunction, fibrosis and cell signaling abnormalities.

Bile acids (BAs) are the main active ingredients of many natural products, especially bile or gallstones in animals, which are widely used in traditional medicine. For example, calculus bovis (bovine gallstones) is commonly used to reduce inflammation and to treat cardiovascular diseases in traditional medicine. Besides natural BAs, some synthetic medicine are also applied to many diseases, for instance, the synthesized ursodeoxycholic acid is used in the treatment of diverse hepatobiliary disorders, including cholestatic liver disease and steroidal gallstone. Certain BAs also play the role in modulating molecular signaling pathways and substrate metabolism by activating farnesoid X receptor (FXR). Due to the regulatory effect of FXR on inflammation, mitochondrial dysfunction and oxidative stress, the treatment with BAs and FXR agonists for metabolic syndrome and DCM have gained more attention. This review will focus on the role of inflammation, mitochondrial dysfunction and oxidative stress in the pathogenesis of DCM and the regulatory effect of BAs and FXR.

2. BAs METABOLISM AND FXR

Primary BAs are synthesized by cholesterol within the liver and conjugated with taurine and glycine. Primary BAs are conjugated with the amino acids taurine or glycine before they are secreted into the bile canalicular. Conjugation of BAs is conductive to increase the BAs hydrophilicity and decrease the lipid toxicity. BAs are stored in the gallbladder and secreted into the intestine after a meal. Primary BAs are subjected to a series of structural modifications and metabolized to secondary BAs by bacterial enzymes [11]. Following this step, a variety of primary BAs and secondary BAs make up the bile acid pool which is necessary for the lipid solubilization and absorption in the enterohepatic cycle. About 95% of the bile acid pool are reabsorbed from

intestine return to liver through the enterohepatic cycle. The remaining 5% of the pool are excreted in the feces and replaced by de novo synthesis [12].

FXR is a member of nuclear receptor superfamily which is described by Forman in 1995 [13]. FXR was found to be activated by primary BAs such as chenodeoxycholic acid (CDCA), cholic acid (CA) and synthetic agonists such as obeticholic acid (OCA) [14] and then plays a critical role in regulating lipid metabolism, glucose metabolism, oxidative stress and inflammation [15, 16]. After activation, FXR binds to FXR response elements (FXREs) or forms heterodimers with the 9-cis-retinoic acid receptor (RXR), regulating the transcription of target genes involved in BAs synthesis, conjugation, absorption and secretion [16, 17]. FXR can also activate the small heterodimer partner (SHP) to inhibit the expression of liver receptor homolog, liver X receptor, and then resulting in inhibiting the transcription of cholesterol 7a-hydroxylase (CYP7A1), which is the rate-limiting enzyme of bile acid synthesis and cholesterol metabolism [18, 19]. Moreover, BAs is closely related to the homeostasis of triglycerides as the interruption of the enterohepatic circulation of bile acids result in elevated plasma triglyceride levels. It has demonstrated that FXR activated SHP to regulate fatty acids and triglycerides biosynthesis via inhibiting the expression of Acetyl-CoA Synthetase (AceCs), Malic Enzyme (ME) and Stearoyl-CoA Desaturase-1 (Scd-1) [11].

FXR is wildly expressed in several tissues, such as liver, intestines, kidney and adrenals. Recent studies have demonstrated that FXR is also expressed in adult cardiomyocytes, heart tissues and different cell types of the vascular wall [20, 21]. Except the effect on control of bile acid synthesis and cholesterol metabolism, FXR is also involved in various physiological and pathological processes of cardiovascular diseases, including inflammatory response, oxidative stress, apoptosis and vascular remodeling. Recently, numerous studies have demonstrated the role of FXR in cardiovascular system [22, 23]. It has been reported that activation of FXR boosted reverse cholesterol transport through inhibiting hepatic CYP7A1 and prevented the development of atherosclerosis [23]. Moreover, FXR ligand has been found to play a positive role in reducing cardiomyocytes apoptosis, fibrosis and restoring heart insulin signaling [24]. Conclusively, FXR has been considered as a novel key-target for the treatment of cardiovascular diseases including cardiomyopathy and atherosclerosis.

3. INFLAMMATION AND DCM

3.1 Role of Inflammation in the Pathogenesis of DCM

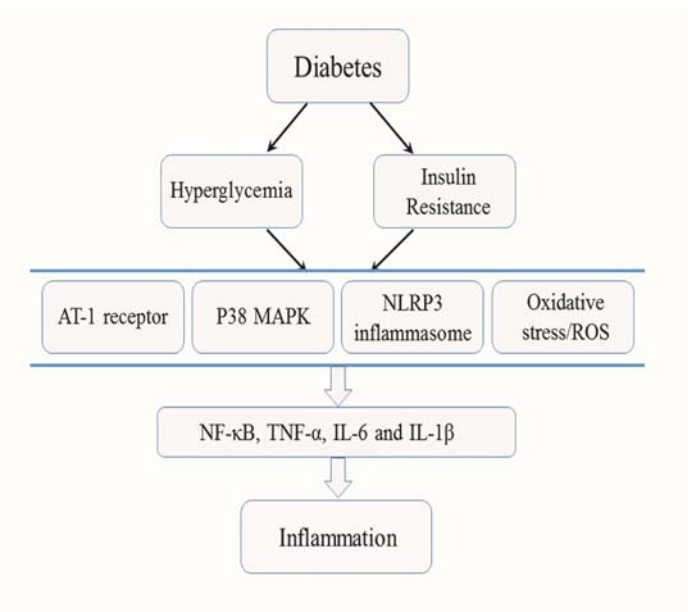
Both clinic study and animal models have demonstrated that an increased inflammation was involved in the pathologic process of DCM [25-27]. Increased expression of proinflammatory cytokines, such as, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), tumor necrosis factor (TNF-α), IL-6 and IL-1β contribute to inflammatory injury, myocardial remodeling and cardiac diastolic dysfunction, and nuclear factor (NF)-κB is responsible for the expression or activation of proinflammatory cytokines [6, 5, 28]. Mouse or rat models of DM have demonstrated that inhibition expression of proinflammatory cytokines attenuated left ventricular dysfunction and cardiac fibrosis [28, 29]. On the other hand, it have been shown that the anti-inflammatory treatments or interventions not only decreased the inflammatory injury, but also attenuated oxidative stress, remodeling and cardiac dysfunction in DCM [30, 31].

Angiotensin-1 (AT-1) receptor, p38 mitogen-activated protein kinase (MAPK) signaling pathway, NOD-like receptor pyrindomain-containing-3 (NLRP3) inflammasome and oxidative stress induced by ROS have been recognized as the major contributors of inflammatory response in DCM (Fig. **1**) [6, 32, 33]. Irbesartan, an AT-1 receptor antagonist, was reported to reduce the level of proinflammatory cytokines (TNF-α, TGF-β and IL-1β) and attenuate cardiac fibrosis in STZ-induced diabetic mice [33]. TNF-α activates p38 MAPK signaling pathway, which then mediates inflammatory damage and cell apoptosis in DCM [34]. Inhibition of p38 MAPK attenuated the left ventricular dysfunction through decreasing the expression of proinflammatory cytokines in DCM mouse models [35]. Increasing evidence reveals that NLRP3 inflammasome might be a novel molecular marker in DCM [5, 36]. It is also known, that NLRP3 inflammasome expressed abundantly in cardiomyocytes, played a critical role in cell death [36]. Recent studies have indicated that the expression of NLRP3 inflammasome was increased under conditions of hyperglycemia and lipid accumulation in DM and obesity [37, 38]. Furthermore, NF-κB was found to involve in the transcriptional induction and activation of the NLRP3 inflammasome [39, 40]. One of NLRP3 inflammasome function is to process pro-IL-18 and pro-IL-1β into the mature forms (IL-18 and IL-1β), which are considered as the main risk factors of myocardial inflammatory injury and cardiomyocytes apoptosis in DCM [35]. Activation of NLRP3 inflammasome results in caspase-1 processing and activation, which cleaves gasdermin D into two fragments and induces the lytic pro-inflammation cell death known as pyroptosis [41, 42]. A complex relationship exists between oxidative stress and inflammation, in which increased ROS production resulted in the increased expression of inflammatory cytokines, and conversely, high level of inflammatory cytokines can promote the production of ROS [32]. ROS generation induced by hyperglycemia could activate NF-κB and thioredoxin interacting/inhibiting protein (TXNIP), which account for the increased NLRP3 inflammasome expression in DCM [43, 44].

Fig. (1). Inflammation is involved in the pathologic process of DCM. Under the hyperglycemia and insulin resistance condition in diabetes, activation of angiotensin-1 (AT-1) receptor and p38 MAPK signaling pathway, increased of NOD-like receptor pyrindomain-containing-3 (NLRP3) inflammasome and oxidative stress induce the expression of proinflammatory cytokines, resulting in inflammatory response in DCM.

3.2 The effect of BAs and FXR on inflammation

A recent experimental study has revealed that FXR-/- mice had a higher TNF-α mRNA level compared with wide-type mice fed the same chow diet [45]. Besides that, FXR-/- mice fed high fat diet had a dramatic increased TNF-α level



compared with wide-type mice fed normal diet [45]. These findings showed that loss of functional FXR results in increased inflammation. On the other hand, it has also been reported that both natural and synthetic FXR ligands inhibited the production of IL-1β, IL-6, and TNF-α from macrophage in response to LPS-induced Toll-like receptor (TLR-4) activation, but that is not the case in FXR-/- mice [46]. Moreover, FXR activation showed a vital role in regulating cardiovascular inflammatory response. There is no doubt that NF-κB is considered an important regulator of the inflammatory response. Activated NF-κB enters the nucleus and binds to DNA, thereby inducing the transcription of TNF-α, IL-6, inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2. The inhibitory effect of FXR activation on hepatic inflammation via suppressing NF-κB signaling has been confirmed [47]. Recent study has demonstrated that activation of FXR and SHP in vascular smooth muscle cells (VSMC) suppressed IL-1β-induced NF-κB activation and reduced the expression of iNOS and COX-2 which contributed to vascular inflammation, VSMC migration and atherosclerosis lesions [22]. FXR agonist CDCA treatment decreased the blood pressure through increasing eNOS and NO production and reducing endothelin-1 (ET-1) expression [48]. In addition, FXR activation inhibited the inflammatory response through suppressing the activation of NF-κB and expression of VCAM-1 [48]. To summarize, these data suggest that FXR ligands (BAs) play a potential role in attenuating inflammation in cardiovascular diseases such as atherosclerosis and cardiomyopathy.

4. MITOCHONDRIAL DYSFUNCTION AND DCM

4.1 Role of Mitochondrial Dysfunction in the Pathogenesis of DCM

It is well known that about 90% of intracellular ATP is provided by mitochondrial oxidative phosphorylation in cardiomyocytes [9], thus mitochondrial dysfunction plays a critical role in the development of cardiomyopathy. Though less studies provided direct evidence for mitochondrial dysfunction in diabetic patients, a number of animal models has directly demonstrated that cardiac mitochondrial dysfunction is a major risk factor for myocardial damage, remodeling and the development of DCM [49]. Interestingly, myocardial contractile dysfunction was associated with mitochondrial dysfunction in type 2 diabetic patients but not in obese patients who were only in the early stage of insulin resistant [50]. This means that mitochondrial dysfunction rather than insulin resistant might be the main culprit factor of DCM. Increased mitochondrial number has been found in diabetic cardiomyocytes, suggesting a compensative response to overcome impaired mitochondrial function [51, 52].

Glucose and free fatty acid (FFA) are the two major energy production sources for cardiomyocytes. However, FFA oxidation turn to the major source of ATP production due to the insulin resistance and hyperglycemia in DM, accompanied by impaired mitochondrial oxidative phosphorylation and increased ROS generation [5, 9, 53]. Physiologically, complexes I and III in the electron transport chain are the major place for the production of mitochondrial ROS. Under hyperglycemia and insulin resistance conditions, increased flux of electron transfer donors to the mitochondrial respiratory chain results in hyperpolarization of the mitochondrial inner membrane, and then inhibits electron transport in complex III which lead to an excess generation of ROS [54]. Mitochondrial ROS conversely impaired the mitochondrial function, since mitochondrial DNA is more sensitive to oxidative damage induced by ROS [54].

Impaired Ca2+ handling is also a vital promoter of the mitochondrial respiratory dysfunction. Calcium plays a critical role in regulating the activation of metabolic enzymes and the production of ATP, as well as impaired mitochondrial Ca2+ uptake and handling in cardiomyocytes was reported in DM [55, 56]. Some studies have shown that mitochondria in diabetic cardiomyocytes are sensitive to mitochondrial permeability transition pores (mPTP) opening, which could be induced by impaired mitochondrial Ca2+ handling, resulting in cardiomyocytes necrosis [57]. In addition, mitochondrial function is closely related with mitochondrial biogenesis. Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α served as an important role in mitochondrial biogenesis, calcium signaling and regulation of respiratory activity [58]. Recent study has reported that PGC-1α was involved in mitochondrial dysfunction in DCM, since PGC-1α is known to mediate the mitochondrial number and the expression of PGC-1α is decreased at later stages of diabetes [49, 59].

4.2 The effect of BAs and FXR on mitochondrial dysfunction

FXR is a critical regulator of glucose and lipid metabolism which are closely linked to mitochondrial function. Previous study has demonstrated that FXR activation reduced the mitochondrial dysfunction and oxidative stress, which thereby inhibited the hepatic fibrosis [60]. Emerging study has shown that FXR agonist CDCA treatment in cardiomyocytes upregulated some genes involved in β-oxidation and mitochondrial function such as malonyl-CoA decarboxylase (MCD), AOX, PDK-4 and uncoupling protein (UCP)-3 [24]. However, a recent study has reported that FXR activation promoted mPTP opening, cytochrome c release, and reduced mitochondrial membrane

potential, which thereby induced the mitochondrial dysfunction and cardiomyocytes apoptosis [20]. Conversely, our recent data have indicated that FXR activation protected against myocardial damage induced by hyperlipidemia or palmitic acid, which was also consistent with another study [24]. In addition, it was reported that FXR activation rescued the post-myocardial infarction cardiac dysfunction and remodeling via increased mitochondrial biogenesis and reduced myocardial inflammation [61]. The further mechanism study has shown that FXR activation increased atrial natriuretic peptide (ANP) expression and secretion, which increased phosphorylation of AMPK and expression of PGC-1α in cardiomyocytes [57].

Autophagy is a dynamic and highly conserved cellular catabolic process that degrades damaged organelles and proteins to keep cellular homeostasis [62]. Increased evidences have demonstrated that autophagy is closely linked to the mitochondrial function, especially the mitophagy [63]. It was reported that CREB is a novel transcriptional activator of autophagy and FXR activation may inhibit the CREB activity, resulting in suppressing hepatic autophagy after feeding [64]. However, one other study has shown that FXR deficiency reduced the activation of forkhead Box O3a which was induced by ethanol, and then repressed the autophagy process [65]. To summarize, FXR shows a critical regulatory effect on autophagy and mitochondrial function.

5. OXIDATIVE STRESS AND DCM

5.1 Role of Oxidative Stress in the Pathogenesis of DCM

Oxidative stress has been regarded as the main criminals in the onset of DM and DCM. It was demonstrated that oxidative damage induced by reactive oxygen or nitrogen species (ROS or RNS) of myocardium played a critical role in the early pathologic alterations of DCM [28, 66, 67]. Oxidative modification of DNA, protein and lipid by excess ROS is closely associated with some potentially harmful aberrations including protein degradation, local or global unfolding and dissociation of catalytic subunits of enzymes in DCM [28]. In addition, a state of hyperglycemia or fluctuating blood glucose levels can induce acute oxidative stress that might be the key factor for the early pathologic alterations of DCM [68]. Increased oxidative stress in diabetes is also involved in cardiomyocytes inflammation, apoptosis and myocardial dysfunction even diabetic heart failure.

Impaired glucose uptake and inappropriate glycogenolysis and gluconeogenesis increase plasma glucose levels promoting the ROS synthesis, thus hyperglycemia is considered as the major promoter for the synthesis of ROS in the diabetic heart, and advanced glycation end-products (AGEs), nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase, xanthine oxidase (XO), uncoupling of nitric oxide synthase (NOS), lipoxygenase enzymes and mitochondrial electron transport chain (ETC) have also been reported to contribute to generate ROS (Fig. **2**) [69, 70]. As a major intracellular source of ATP synthesis, mitochondria generate excessive ROS as a result of promoting oxidative metabolic flux under conditions of hyperglycemia. In another case, saturated ETC in hyperglycemia will force electrons to be transfered to molecular oxygen and form superoxide within mitochondria, since the ability of ETC to transfer electrons depends on intracellular glucose concentration [71]. The hyperglycemic state in diabetes induces citric acid cycle hyperactivity to promote the glucose metabolism, which inevitably generate excessive superoxide at complex I and complex III in ETC70. Excessive superoxide also induces ETC uncoupling resulting in swelling of the mitochondrial matrix and further superoxide generation to produce oxidative stress [72].

Recent studies have demonstrated that NAPDH oxidases are responsible for large amounts of ROS generation by non-mitochondrial source. Activity or expression of NAPDH oxidases in the diabetic heart has been reported to be significantly higher [73-75]. It was reported that superoxide production was significantly reduced in cardiac-specific NOX4 knockout mice, indicating that NOX4 was a major source of the generation of superoxide [76]. In addition, hyperglycemia-induced NAPDH oxidases activation produces superoxide which can combine with nitric oxide (NO), producing more harmful peroxynitrite species [67]. The specific role of XO in the pathogenesis of DCM is not well clear, but inhibition of XO significantly decreased myocardial ROS generation and iNOS expression, attenuating the cardiomyocytes apoptosis and fibrosis in type I diabetic mouse [77]. Uncoupling of NOS leads to increased ROS generation and decreased NO bioavailability since uncoupled NOS produces more superoxide anion instead of NO. Therefore, the uncoupling of NOS increases oxidative stress and is implicated in the pathological changes of DCM. Lipoxygenases are a family of enzymes that oxidatively metabolise arachidonic acid into hydroperoxides. 12/15 lipoxygenases are closely related with ROS production. It has been reported that activation of 12/15 lipoxygenases resulted in increased oxidative stress and promoting the pathogenesis progress of DCM [65].

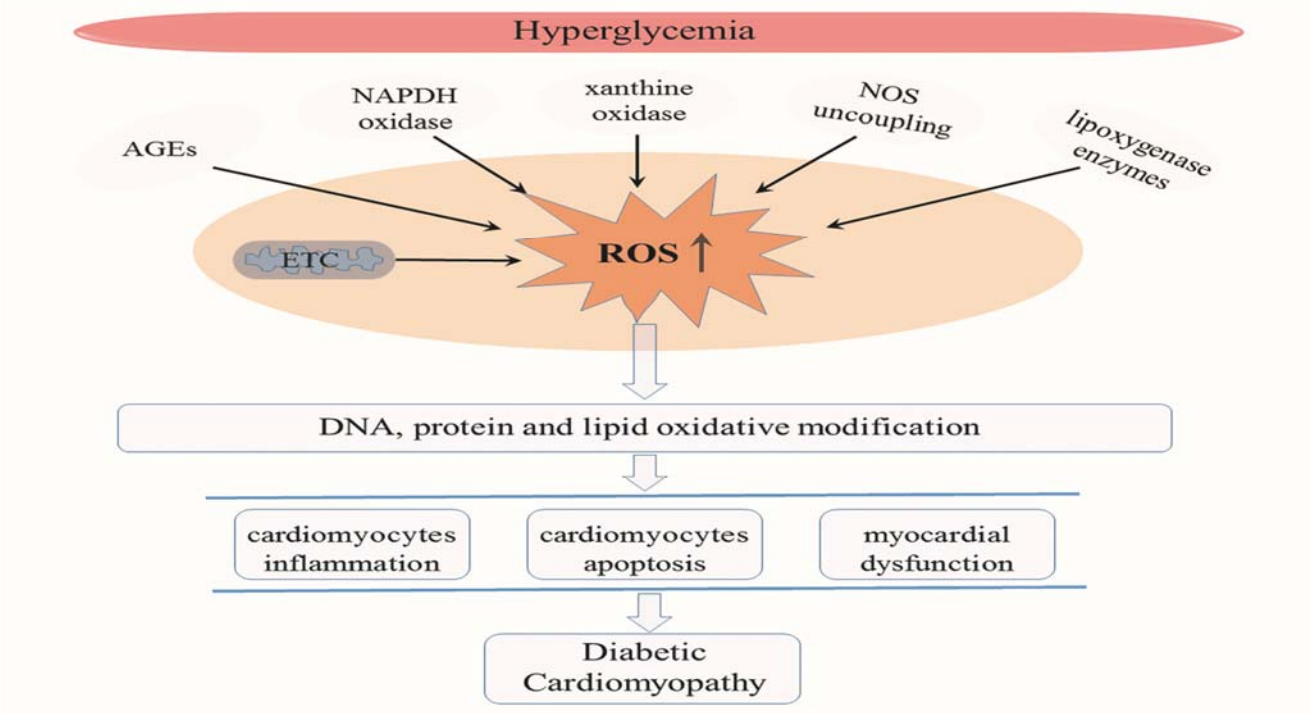


Fig. (2). Oxidative stress induced by ROS plays a critical role in the pathologic alterations of DCM. Under the hyperglycemia condition, advanced glycation end-products (AGEs), nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase, xanthine oxidase (XO), uncoupling of nitric oxide synthase (NOS), lipoxygenase enzymes and mitochondrial electron transport chain (ETC) contribute to generate excessive ROS. Oxidative modification of DNA, protein and lipid by excess ROS result in cardiomyocytes inflammation, apoptosis and myocardial dysfunction.

5.2 The Effect of BAs and FXR on Oxidative Stress

Recent studies have shown that FXR plays a positive role in suppressing oxidative stress. Jun Pu et al. has reported that the expression of FXR and SHP in neonatal rat ventricular myocytes exposed to H2O2 significantly increased, indicating myocytes exhibit a response to ROS with an activation in FXR [20]. Another study showed that activation of FXR by CDCA in rat heart upregulated the expression of some genes involved in β-oxidation such as acyl-CoA oxidase and pyruvate dehydrogenase kinase. Moreover, FXR activation also reduced lipid content, attenuated the cardiomyocytes apoptosis and restored heart insulin signaling [24]. It is well known that the bioactivity of NOS and NO are closely related to the ROS production. Recent works have demonstrated that activation of FXR in vascular endothelial cells increased the expression of endothelial NOS and NO, which indicated the regulatory effect of FXR activation on endothelial oxidative stress [78]. In addition, our group and others demonstrated that activation of FXR attenuated oxidative stress characterized by the increased level of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), decreased level of malondialdehyde (MDA) and ROS in both mouse liver and kidney [79, 80]. Further study has demonstrated that the regulatory effect of FXR on oxidative stress might be related to the phosphorylation of AMP-activated protein kinase (AMPK) and the activation of nuclear erythroid factor 2-related factor 2 (Nrf2) [81]. Nrf2 has been found to mediate in the inhibitory effect of FXR on cellular oxidative stress [79, 82, 83]. FXR activation increased AMPK phosphorylation and Nrf2 expression, resulting in decreased ROS level and increased levels of SOD and GSH-Px [77]. Nrf2 acts a key role in regulating intracellular redox homeostasis via enhancing antioxidant capacity and reducing ROS-induced damage [84, 85]. Furthermore, Nrf2 also can translocate from cytosol to nucleus resulting in activating the phase II antioxidants such as heme oxygenase-1 (HO-1) and glutathione S-transferase (GST), which also protect cells from ROS [86].

CONCLUSION

The features of DCM are characterized by cardiomyocytes apoptosis, myocardial fibrosis, remodeling and cardiac dysfunction. Hyperglycemia and insulin resistance serve as the pivotal factors in the pathogenesis of DCM, which also involved oxidative stress, inflammation and mitochondrial dysfunction. There is no doubt that the pathogenesis of DCM is multifactorial, eventually resulting in cardiac dysfunction and heart failure. BAs, synthesizing from cholesterol in the hepatocyte, binds FXR to conversely regulate the synthesis and metabolism of BAs. In addition, FXR activation also participates in the pathological of many diseases, such as alcoholic liver disease, nonalcoholic fatty liver disease, cardiovascular diseases and carcinogenesis. Increased evidences have demonstrated that BAs and FXR play a vital role in regulating lipid metabolism, glucose metabolism,

oxidative stress, inflammation and mitochondrial function, showing a potential therapeutic effect for DCM. However, further studies are essential to reveal the precise mechanisms of FXR in DCM treatment and to explore novel therapeutic strategies.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This work was supported by National Nature Science Foundation of China grant nos. 81473653 and 81774242.

REFERENCES

[1] Cho, N. H.; Shaw, J. E.; Karuranga, S.; Huang, Y.; da Rocha Fernandes, J. D.; Ohlrogge, A. W.; Malanda, B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res. Clin. Pract.*, **2018**, *138*, 271-281.

[2] New WHO statistics highlight increases in blood pressure and diabetes, other noncommunicable risk factors. *Cent. Eur. J. Public Health.*, **2012**, *20*(2), 134, 149.

[3] Rubler, S.; Dlugash, J.; Yuceoglu, Y. Z.; Kumral, T.; Branwood, A. W.; Grishman, A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am. J. Cardiol.*, **1972**, *30*(6), 595-602.

[4] Kannel, W. B.; Hjortland, M.; Castelli, W. P. Role of diabetes in congestive heart failure: the Framingham study. *Am. J. Cardiol.*, **1974**, *34*(1), 29-34.

[5] Jia, G.; Hill, M. A.; Sowers, J. R. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity. *Circ. Res.*, **2018**, *122*(4), 624-638.

[6] Hu, X.; Bai, T.; Xu, Z.; Liu, Q.; Zheng, Y.; Cai, L. Pathophysiological Fundamentals of Diabetic Cardiomyopathy. *Compr. Physiol.*, **2017**, *7*(2), 693-711.

[7] Sandesara, P. B.; O'Neal, W. T.; Kelli, H. M. Samman-Tahhan, A.; Hammadah, M.; Quyyumi, A. A.; Sperling, L. S. The Prognostic Significance of Diabetes and Microvascular Complications in Patients With Heart Failure With Preserved Ejection Fraction. *Diabetes Care.*, **2018**, *41*(1), 150-155.

[8] Maisch, B.; Alter, P.; Pankuweit, S. Diabetic cardiomyopathy--fact or fiction? *Herz*, **2011**, *36*(2), 102-115.

[9] Jia, G.; DeMarco, V. G.; Sowers, J. R. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. *Nat. Rev. Endocrinol.*, **2016**, *12*(3), 144-153.

[10] Russo, I.; Frangogiannis, N. G. Diabetes-associated cardiac fibrosis: Cellular effectors, molecular mechanisms and therapeutic opportunities. *J. Mol. Cell Cardiol.*, **2016**, *90*, 84-93.

[11] Martinot, E.; Sedes, L.; Baptissart, M.; Lobaccaro, J. M.; Caira, F.; Beaudoin, C.; Volle, D. H. Bile acids and their receptors. *Mol. Aspects. Med.*, **2017**, *56*, 2-9.

[12] Spinelli, V.; Chavez-Talavera, O.; Tailleux, A.; Staels, B. Metabolic effects of bile acid sequestration: impact on cardiovascular risk factors. *Curr. Opin. Endocrinol. Diabetes Obes.*, **2016**, *23*(2), 138-144.

[13] Forman, B. M.; Goode, E.; Chen, J.; Oro, A. E.; Bradley, D. J.; Perlmann, T.; Noonan, D. J.; Burka, L. T.; McMorris, T.; Lamph, W. W.; Evans, R. M.; Weinberger, C. Identification of a nuclear receptor that is activated by farnesol metabolites. *Cell*, **1995**, *81*(5), 687-693.

[14] Moris, D.; Giaginis, C.; Tsourouflis, G.; Theocharis, S. Farnesoid-X Receptor (FXR) as a Promising Pharmaceutical Target in Atherosclerosis. *Curr. Med. Chem.*, **2017**, *24*(11), 1147-1157.

[15] Hageman, J.; Herrema, H.; Groen, A. K.; Kuipers, F. A role of the bile salt receptor FXR in atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.*, **2010**, *30*(8), 1519-1528.

[16] Porez, G.; Prawitt, J.; Gross, B.; Staels, B. Bile acid receptors as targets for the treatment of dyslipidemia and cardiovascular disease. *J. Lipid Res.*, **2012**, *53*(9), 1723-1737.

[17] Ali, A. H.; Carey, E. J.; Lindor, K. D. Recent advances in the development of farnesoid X receptor agonists. *Ann. Transl. Med.*, **2015**, *3*(1), 5.

[18] Brendel, C.; Schoonjans, K.; Botrugno, O. A.; Treuter, E.; Auwerx, J. The small heterodimer partner interacts with the liver X receptor alpha and represses its transcriptional activity. *Mol. Endocrinol.*, **2002**, *16*(9), 2065-2076.

[19] De Fabiani, E.; Mitro, N.; Anzulovich, A. C.; Pinelli, A.; Galli, G.; Crestani, M. The negative effects of bile acids and tumor necrosis factor-alpha on the transcription of cholesterol 7alpha-hydroxylase gene (CYP7A1) converge to hepatic nuclear factor-4: a novel mechanism of feedback regulation of bile acid synthesis mediated by nuclear receptors. *J. Biol. Chem.*, **2001**, *276*(33), 30708-30716.

[20] Pu, J.; Yuan, A.; Shan, P.; Gao, E.; Wang, X.; Wang, Y.; Lau, W. B.; Koch, W.; Ma, X. L.; He, B. Cardiomyocyte-expressed farnesoid-X-receptor is a novel apoptosis mediator and contributes to myocardial ischaemia/reperfusion injury. *Eur. Heart. J.*, **2013**, *34*(24), 1834-1845.

[21] He, F.; Li, J.; Mu, Y.; Kuruba, R.; Ma, Z.; Wilson, A.; Alber, S.; Jiang, Y.; Stevens, T.; Watkins, S.; Pitt, B.; Xie, W.; Li, S. Downregulation of endothelin-1 by farnesoid X receptor in vascular endothelial cells. *Circ. Res.*, **2006**, *98*(2), 192-199.

[22] Li, Y. T.; Swales, K. E.; Thomas, G. J.; Warner, T. D.; Bishop-Bailey, D. Farnesoid x receptor ligands inhibit vascular smooth muscle cell inflammation and migration. *Arterioscler. Thromb. Vasc. Biol.*, **2007**, *27*(12), 2606-2611.

[23] Xu, Y.; Li, F.; Zalzala, M.; Xu, J.; Gonzalez, F. J.; Adorini, L.; Lee, Y. K.; Yin, L.; Zhang, Y. Farnesoid X receptor activation increases reverse cholesterol transport by modulating bile acid composition and cholesterol absorption in mice. *Hepatology*, **2016**, *64*(4), 1072-1085.

[24] Mencarelli, A.; Cipriani, S.; Renga, B.; D'Amore, C.; Palladino, G.; Distrutti, E.; Baldelli, F.; Fiorucci, S. FXR activation improves myocardial fatty acid metabolism in a rodent model of obesity-driven cardiotoxicity. *Nutr. Metab. Cardiovasc. Dis.*, **2013**, *23*(2), 94-101.

[25] Diamant, M.; Lamb, H. J.; Smit, J. W.; de Roos, A.; Heine, R. J. Diabetic cardiomyopathy in uncomplicated type 2 diabetes is associated with the metabolic syndrome and systemic inflammation. *Diabetologia,* **2005**, *48*(8), 1669-1670.

[26] Song, Y.; Wang, J.; Li, Y.; Du, Y.; Arteel, G. E.; Saari, J. T.; Kang, Y. J.; Cai, L. Cardiac metallothionein synthesis in streptozotocin-induced diabetic mice, and its protection against diabetes-induced cardiac injury. *Am. J. Pathol.*, **2005**, *167*(1), 17-26.

[27] Tschope, C.; Walther, T.; Escher, F.; Spillmann, F.; Du, J.; Altmann, C.; Schimke, I.; Bader, M.; Sanchez-Ferrer, C. F.; Schultheiss, H. P.; Noutsias, M. Transgenic activation of the kallikrein-kinin system inhibits intramyocardial inflammation, endothelial dysfunction and oxidative stress in experimental diabetic cardiomyopathy. *FASEB J.*, **2005**, *19*(14), 2057-2059.

[28] Varga, Z. V.; Giricz, Z.; Liaudet, L.; Hasko, G.; Ferdinandy, P.; Pacher, P. Interplay of oxidative, nitrosative/nitrative stress, inflammation, cell death and autophagy in diabetic cardiomyopathy. *Biochim. Biophys. Acta.*, **2015**, *1852*(2), 232-242.

[29] Westermann, D.; Walther, T.; Savvatis, K.; Escher, F.; Sobirey, M.; Riad, A.; Bader, M.; Schultheiss, H. P.; Tschope, C., Gene deletion of the kinin receptor B1 attenuates cardiac inflammation and fibrosis during the development of experimental diabetic cardiomyopathy. *Diabetes*, **2009**, *58*(6), 1373-1381.

[30] Rajesh, M.; Mukhopadhyay, P.; Batkai, S.; Patel, V.; Saito, K.; Matsumoto, S.; Kashiwaya, Y.; Horvath, B.; Mukhopadhyay, B.; Becker, L.; Hasko, G.; Liaudet, L.; Wink, D. A.; Veves, A.; Mechoulam, R.; Pacher, P. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell

death signaling pathways in diabetic cardiomyopathy. *J. Am. Coll. Cardiol.*, **2010**, *56*(25), 2115-2125.

[31] Westermann, D.; Van Linthout, S.; Dhayat, S.; Dhayat, N.; Schmidt, A.; Noutsias, M.; Song, X. Y.; Spillmann, F.; Riad, A.; Schultheiss, H. P.; Tschope, C. Tumor necrosis factor-alpha antagonism protects from myocardial inflammation and fibrosis in experimental diabetic cardiomyopathy. *Basic. Res. Cardiol.*, **2007**, *102*(6), 500-507.

[32] Sharma, A.; Tate, M.; Mathew, G.; Vince, J. E.; Ritchie, R. H.; de Haan, J. B. Oxidative Stress and NLRP3-Inflammasome Activity as Significant Drivers of Diabetic Cardiovascular Complications: Therapeutic Implications. *Front. Physiol.*, **2018**, *9*, 114.

[33] Westermann, D.; Rutschow, S.; Jager, S.; Linderer, A.; Anker, S.; Riad, A.; Unger, T.; Schultheiss, H. P.; Pauschinger, M.; Tschope, C. Contributions of inflammation and cardiac matrix metalloproteinase activity to cardiac failure in diabetic cardiomyopathy: the role of angiotensin type 1 receptor antagonism. *Diabetes*, **2007**, *56*(3), 641-646.

[34] Klein, J. B.; Wang, G. W.; Zhou, Z.; Buridi, A.; Kang, Y. J. Inhibition of tumor necrosis factor-alpha-dependent cardiomyocyte apoptosis by metallothionein. *Cardiovasc. Toxicol*, **2002**, *2*(3), 209-218.

[35] Westermann, D.; Rutschow, S.; Van Linthout, S.; Linderer, A.; Bucker-Gartner, C.; Sobirey, M.; Riad, A.; Pauschinger, M.; Schultheiss, H. P.; Tschope, C. Inhibition of p38 mitogen-activated protein kinase attenuates left ventricular dysfunction by mediating pro-inflammatory cardiac cytokine levels in a mouse model of diabetes mellitus. *Diabetologia*, **2006**, *49*(10), 2507-2513.

[36] Luo, B.; Huang, F.; Liu, Y.; Liang, Y.; Wei, Z.; Ke, H.; Zeng, Z.; Huang, W.; He, Y. NLRP3 Inflammasome as a Molecular Marker in Diabetic Cardiomyopathy. *Front. Physiol.*, **2017**, *8*, 519.

[37] Jin, C.; Flavell, R. A. Innate sensors of pathogen and stress: linking inflammation to obesity. *J. Allergy. Clin. Immunol.*, **2013**, *132*(2), 287-294.

[38] Wen, H.; Gris, D.; Lei, Y.; Jha, S.; Zhang, L.; Huang, M. T.; Brickey, W. J.; Ting, J. P. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. *Nat. Immunol.*, **2011**, *12*(5), 408-415.

[39] Liao, P. C.; Chao, L. K.; Chou, J. C.; Dong, W. C.; Lin, C. N.; Lin, C. Y.; Chen, A.; Ka, S. M.; Ho, C. L.; Hua, K. F. Lipopolysaccharide/adenosine triphosphate-mediated signal transduction in the regulation of NLRP3 protein expression and caspase-1-mediated interleukin-1beta secretion. *Inflamm. Res.*, **2013**, *62*(1), 89-96.

[40] Luo, B.; Li, B.; Wang, W.; Liu, X.; Xia, Y.; Zhang, C.; Zhang, M.; Zhang, Y.; An, F. NLRP3 gene silencing ameliorates diabetic cardiomyopathy in a type 2 diabetes rat model. *PloS one*, **2014**, *9*(8), e104771.

[41] Liu, X.; Zhang, Z.; Ruan, J.; Pan, Y.; Magupalli, V. G.; Wu, H.; Lieberman, J., Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. *Nature*, **2016**, *535*(7610), 153-158.

[42] Sborgi, L.; Ruhl, S.; Mulvihill, E.; Pipercevic, J.; Heilig, R.; Stahlberg, H.; Farady, C. J.; Muller, D. J.; Broz, P.; Hiller, S., GSDMD membrane pore formation constitutes the mechanism of pyroptotic cell death. *EMBO j*., **2016**, *35*(16), 1766-1778.

[43] Franchi, L.; Munoz-Planillo, R.; Nunez, G. Sensing and reacting to microbes through the inflammasomes. *Nat. Immunol.*, **2012**, *13*(4), 325-332.

[44] Kumar, S.; Prasad, S.; Sitasawad, S. L. Multiple antioxidants improve cardiac complications and inhibit cardiac cell death in streptozotocin-induced diabetic rats. *PloS one*, **2013**, *8*(7), e67009.

[45] Hanniman, E. A.; Lambert, G.; McCarthy, T. C.; Sinal, C. J. Loss of functional farnesoid X receptor increases atherosclerotic lesions in apolipoprotein E-deficient mice. *J. Lipid. Res.*, **2005**, *46*(12), 2595-2604.

[46] Mencarelli, A.; Renga, B.; Distrutti, E.; Fiorucci, S. Antiatherosclerotic effect of farnesoid X receptor. *Am. J. Physiol. Heart Circ. Physiol.*, **2009**, *296*(2), H272-81.

[47] Gai, Z.; Visentin, M.; Gui, T.; Zhao, L.; Thasler, W. E.; Hausler, S.; Hartling, I.; Cremonesi, A.; Hiller, C.; Kullak-Ublick, G. A., Effects of Farnesoid X Receptor Activation on Arachidonic Acid Metabolism, NF-kB Signaling, and Hepatic Inflammation. *Mol. Pharmacol.,* **2018**, *94*(2), 802-811.

[48] Li, C.; Li, J.; Weng, X.; Lan, X.; Chi, X. Farnesoid X receptor agonist CDCA reduces blood pressure and regulates vascular tone in spontaneously hypertensive rats. *J. Am. Soc. Hypertens.*, **2015**, *9*(7), 507-516 e7.

[49] Duncan, J. G., Mitochondrial dysfunction in diabetic cardiomyopathy. *Biochim. Biophys. Acta.*, **2011**, *1813*(7), 1351-1359.

[50] Montaigne, D.; Marechal, X.; Coisne, A.; Debry, N.; Modine, T.; Fayad, G.; Potelle, C.; El Arid, J. M.; Mouton, S.; Sebti, Y.; Duez, H.; Preau, S.; Remy-Jouet, I.; Zerimech, F.; Koussa, M.; Richard, V.; Neviere, R.; Edme, J. L.; Lefebvre, P.; Staels, B. Myocardial contractile dysfunction is associated with impaired mitochondrial function and dynamics in type 2 diabetic but not in obese patients. *Circulation*, **2014**, *130*(7), 554-564.

[51] Shen, X.; Zheng, S.; Metreveli, N. S.; Epstein, P. N. Protection of cardiac mitochondria by overexpression of MnSOD reduces diabetic cardiomyopathy. *Diabetes*, **2006**, *55*(3), 798-805.

[52] Hafstad, A. D.; Boardman, N.; Aasum, E. How exercise may amend metabolic disturbances in diabetic cardiomyopathy. *Antioxid. Redox. Signal.*, **2015**, *22*(17), 1587-1605.

[53] Yilmaz, S.; Canpolat, U.; Aydogdu, S.; Abboud, H. E. Diabetic Cardiomyopathy; Summary of 41 Years. *Korean. Circ. J.*, **2015**, *45*(4), 266-272.

[54] Teshima, Y.; Takahashi, N.; Nishio, S.; Saito, S.; Kondo, H.; Fukui, A.; Aoki, K.; Yufu, K.; Nakagawa, M.; Saikawa, T. Production of Reactive Oxygen Species in the Diabetic Heart. Roles of mitochondria and NADPH oxidase. *Circ. J.*, **2014**, *78*(2), 300-306.

[55] Saks, V.; Dzeja, P.; Schlattner, U.; Vendelin, M.; Terzic, A.; Wallimann, T. Cardiac system bioenergetics: metabolic basis of the Frank-Starling law. *J. Physiol.*, **2006**, *571*(Pt 2), 253-273.

[56] Fauconnier, J.; Lanner, J. T.; Zhang, S. J.; Tavi, P.; Bruton, J. D.; Katz, A.; Westerblad, H. Insulin and inositol 1,4,5-trisphosphate trigger abnormal cytosolic Ca2+ transients and reveal mitochondrial Ca2+ handling defects in cardiomyocytes of ob/ob mice. *Diabetes*, **2005**, *54*(8), 2375-2381.

[57] Anderson, E. J.; Rodriguez, E.; Anderson, C. A.; Thayne, K.; Chitwood, W. R.; Kypson, A. P. Increased propensity for cell death in diabetic human heart is mediated by mitochondrial-dependent pathways. *Am. J. Physiol. Heart Circ. Physiol.*, **2011**, *300*(1), H118-H124.

[58] Bianchi, K.; Vandecasteele, G.; Carli, C.; Romagnoli, A.; Szabadkai, G.; Rizzuto, R., Regulation of Ca2+ signalling and Ca2+-mediated cell death by the transcriptional coactivator PGC-1alpha. *Cell Death Differ,.* **2006**, *13*(4), 586-96.

[59] Buchanan, J.; Mazumder, P. K.; Hu, P.; Chakrabarti, G.; Roberts, M. W.; Yun, U. J.; Cooksey, R. C.; Litwin, S. E.; Abel, E. D., Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology,* **2005**, *146*(12), 5341-9.

[60] Lee, C. G.; Kim, Y. W.; Kim, E. H.; Meng, Z.; Huang, W.; Hwang, S. J.; Kim, S. G. Farnesoid X receptor protects hepatocytes from injury by repressing miR-199a-3p, which increases levels of LKB1. *Gastroenterology*, **2012**, *142*(5), 1206-1217 e7.

[61] Xia, Y.; Zhang, F.; Zhao, S.; Li, Y.; Chen, X.; Gao, E.; Xu, X.; Xiong, Z.; Zhang, X.; Zhang, J.; Zhao, H.; Wang, W.; Wang, H.; Guo, Y.; Liu, Y.; Li, C.; Wang, S.; Zhang, L.; Yan, W.; Tao, L. Adiponectin Determines Farnesoid X Receptor Agonism-Mediated Cardioprotection Against Post-Infarction Remodeling and Dysfunction. *Cardiovasc. Res.*, **2018**, *114*(10), 1335-1349.

[62] Li, C.; Jiang, F.; Li, Y. L.; Jiang, Y. H.; Yang, W. Q.; Sheng, J.; Xu, W. J.; Zhu, Q. J. Rhynchophylla total alkaloid rescues autophagy, decreases oxidative stress and improves endothelial vasodilation in spontaneous hypertensive rats. *Acta Pharmacol. Sin.*, **2018**, *39*(3), 345-356.

[63] Han, C. Y.; Kim, T. H.; Koo, J. H.; Kim, S. G. Farnesoid X receptor as a regulator of fuel consumption and mitochondrial function. *Arch. Pharm. Res.*, **2016**, *39*(8), 1062-1074.

[64] Seok, S.; Fu, T.; Choi, S. E.; Li, Y.; Zhu, R.; Kumar, S.; Sun, X.; Yoon, G.; Kang, Y.; Zhong, W.; Ma, J.; Kemper, B.; Kemper, J. K. Transcriptional regulation of autophagy by an FXR-CREB axis. *Nature*, **2014**, *516*(7529), 108-111.

[65] Manley, S.; Ni, H. M.; Williams, J. A.; Kong, B.; DiTacchio, L.; Guo, G.; Ding, W. X. Farnesoid X receptor regulates forkhead Box O3a

activation in ethanol-induced autophagy and hepatotoxicity. *Redox. Biol.*, **2014**, *2*, 991-1002.

[66] Pickering, R. J.; Rosado, C. J.; Sharma, A.; Buksh, S.; Tate, M.; de Haan, J. B. Recent novel approaches to limit oxidative stress and inflammation in diabetic complications. *Clin. Transl. Immunology.*, **2018**, *7*(4), e1016.

[67] Liu, Q.; Wang, S.; Cai, L. Diabetic cardiomyopathy and its mechanisms: Role of oxidative stress and damage. *J. Diabetes. Investig.*, **2014**, *5*(6), 623-634.

[68] Giacco, F.; Brownlee, M. Oxidative stress and diabetic complications. *Circ. Res.*, **2010**, *107*(9), 1058-1070.

[69] Kayama, Y.; Raaz, U.; Jagger, A.; Adam, M.; Schellinger, I. N.; Sakamoto, M.; Suzuki, H.; Toyama, K.; Spin, J. M.; Tsao, P. S. Diabetic Cardiovascular Disease Induced by Oxidative Stress. *Int. J. Mol. Sci*., **2015**, *16*(10), 25234-25263.

[70] Faria, A.; Persaud, S. J. Cardiac oxidative stress in diabetes: Mechanisms and therapeutic potential. *Pharmacol. Ther.*, **2017**, *172*, 50-62.

[71] Brownlee, M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*, **2005**, *54*(6), 1615-1625.

[72] Halestrap, A. P. What is the mitochondrial permeability transition pore? *J. Mol. Cell Cardiol.*, **2009**, *46*(6), 821-831.

[73] Rajesh, M.; Batkai, S.; Kechrid, M.; Mukhopadhyay, P.; Lee, W. S.; Horvath, B.; Holovac, E.; Cinar, R.; Liaudet, L.; Mackie, K.; Hasko, G.; Pacher, P. Cannabinoid 1 receptor promotes cardiac dysfunction, oxidative stress, inflammation, and fibrosis in diabetic cardiomyopathy. *Diabetes*, **2012**, *61*(3), 716-727.

[74] Gao, L.; Mann, G. E. Vascular NAD(P)H oxidase activation in diabetes: a double-edged sword in redox signalling. *Cardiovasc. Res.*, **2009**, *82*(1), 9-20.

[75] Roe, N. D.; Thomas, D. P.; Ren, J. Inhibition of NADPH oxidase alleviates experimental diabetes-induced myocardial contractile dysfunction. *Diabetes Obes. Metab.*, **2011**, *13*(5), 465-473.

[76] Kuroda, J.; Ago, T.; Matsushima, S.; Zhai, P.; Schneider, M. D.; Sadoshima, J. NADPH oxidase 4 (Nox4) is a major source of oxidative stress in the failing heart. *Proc. Natl. Acad. Sci. USA*, **2010**, *107*(35), 15565-15570.

[77] Rajesh, M.; Mukhopadhyay, P.; Batkai, S.; Mukhopadhyay, B.; Patel, V.; Hasko, G.; Szabo, C.; Mabley, J. G.; Liaudet, L.; Pacher, P., Xanthine oxidase inhibitor allopurinol attenuates the development of diabetic cardiomyopathy. *J. Cell. Mol. Med.*, **2009**, *13*(8B), 2330-2341.

[78] Li, J.; Wilson, A.; Kuruba, R.; Zhang, Q.; Gao, X.; He, F.; Zhang, L. M.; Pitt, B. R.; Xie, W.; Li, S. FXR-mediated regulation of eNOS expression in vascular endothelial cells. *Cardiovasc. Res.*, **2008**, *77*(1), 169-177.

[79] Dong, L.; Han, X.; Tao, X.; Xu, L.; Xu, Y.; Fang, L.; Yin, L.; Qi, Y.; Li, H.; Peng, J. Protection by the Total Flavonoids from Rosa laevigata Michx Fruit against Lipopolysaccharide-Induced Liver Injury in Mice via Modulation of FXR Signaling. *Foods*, **2018**, *7*(6), pii: E88.

[80] Gai, Z.; Gui, T.; Hiller, C.; Kullak-Ublick, G. A., Farnesoid X Receptor Protects against Kidney Injury in Uninephrectomized Obese Mice. *J. Biol. Chem.,* **2016**, *291*(5), 2397-411.

[81] Jung, E. H.; Lee, J. H.; Kim, S. C.; Kim, Y. W. AMPK activation by liquiritigenin inhibited oxidative hepatic injury and mitochondrial dysfunction induced by nutrition deprivation as mediated with induction of farnesoid X receptor. *Eur. J. Nutr.*, **2017**, *56*(2), 635-647.

[82] Zhang, Y.; Xu, Y.; Qi, Y.; Xu, L.; Song, S.; Yin, L.; Tao, X.; Zhen, Y.; Han, X.; Ma, X.; Liu, K.; Peng, J. Protective effects of dioscin against doxorubicin-induced nephrotoxicity via adjusting FXR-mediated oxidative stress and inflammation. *Toxicology*, **2017**, *378*, 53-64.

[83] Gai, Z.; Chu, L.; Xu, Z.; Song, X.; Sun, D.; Kullak-Ublick, G. A., Farnesoid X receptor activation protects the kidney from ischemia-reperfusion damage. *Sci. Rep.,* **2017**, *7*(1), 9815.

[84] Ge, M.; Yao, W.; Wang, Y.; Yuan, D.; Chi, X.; Luo, G.; Hei, Z. Propofol alleviates liver oxidative stress via activating Nrf2 pathway. *J. Surg. Res.*, **2015**, *196*(2), 373-381.

[85] Weerachayaphorn, J.; Cai, S. Y.; Soroka, C. J.; Boyer, J. L. Nuclear factor erythroid 2-related factor 2 is a positive regulator of human bile salt export pump expression. *Hepatology*, **2009**, *50*(5), 1588-1596.

[86] Chi, X.; Zhang, R.; Shen, N.; Jin, Y.; Alina, A.; Yang, S.; Lin, S. Sulforaphane reduces apoptosis and oncosis along with protecting liver injury-induced ischemic reperfusion by activating the Nrf2/ARE pathway. *Hepatol. Int.*, **2015**, *9*(2), 321-329.